IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Chang-Yi LIN et al.	Confirmation No: 9676
Appl. No.	: 10/800,622	
Filed	: March 16, 2004	
Title	: STABLE AND TASTE MASKED PHARMACEUTICAL DOSAGE FORM USING POROUS APATITE GRAINS	
TC/A.U.	: 1618	
Examiner	: N.G. Ebrahim	
Docket No.:	: LINC3186CIP/REF	
Customer No:	: 23364	

37 CFR §41.37 APPEAL BRIEF

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This brief on appeal for this application is submitted with a Petition for a One Month extension of time and the required fee extending the period for submitting the brief to April 22, 2009. The required appeal fee set forth in §41.20(b)(2) of $540 is also submitted herewith. Any additional fees necessary for this appeal may be charged to Deposit Account No. 02-0200.

41.37 (c)(1)(I) REAL PARTY IN INTEREST

The real party in interest is the Assignee of record, NANOTREND INO-TECH INC

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41.37 (c)(1)(ii) RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences with respect to the claimed invention which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal known to appellant, appellant's legal representative or assignee.

41.37 (c)(1)(iii) STATUS OF THE CLAIMS

This application contains claims 1-72. Claims 17 and 21-71 have been canceled from the application without prejudice or disclaimer and are no longer pending. Claims 1-6, 18-20 and 72 are pending and are the claims on appeal. Claims 1-16, 18-20 and 72 stand finally rejected under 35 USC 103(a) as obvious over the prior art cited and applied in the Final Rejection.

41.37 (c)(1)(iv) STATUS OF AMENDMENTS AFTER FINAL REJECTION

No amendment was filed after Final Rejection. A notice of appeal was filed in response to the Final Rejection.

41.37 (c)(1)(v) SUMMARY OF CLAIMED SUBJECT MATTER

Claim 1 relates to a stable and taste masked pharmaceutical dosage form comprising porous apatite grains and a drug entrapped in pores of said grains, wherein said grains have a size of 0.1-1000 μm and said pores of said grains have an opening of 0.5-300 nm, (page 3, lines 8-12) and said dosage form further comprising a biocompatible polymer, wherein said porous apatite grains are bound by said biocompatible polymer to form a microspherical composite having a size of 0.5-1000 μm. (Page 4, lines 14-16.)

Claim 2 further includes a water soluble polymer entrapped in pores of the grains of the porous apatite in an amount of 0.1-10% based on the weight of the grains as set forth on page 3, lines 18-19.

Claim 12 further defines the dosage form wherein the apatite grains contains carbonate in an amount of 0.1-40% based on the weight of the grains as noted on page 10, lines 5-12 and original claim 12 and claim 13,.wherein the apatite grains have a Ca to P molar ratio of 1.3 to 1.60, page 3, lines 25-26. Claim 16 provides for that the drug is zinc gluconate, copper gluconate, aspirin, ibuprophen or ascorbic acid.

Claim 72 provides for a dosage form of claim 2, wherein the grains have a size of 1 to 300 μm; the pores have an opening of 1 to 200 nm, the grains have a specific surface area of 32 to 58 m^2 per unit gram, the drug entrapped in the porous apatite grains is in an amount of 1-30% based on the weight of the grains, wherein the water soluble polymer is cellulose, polyethylene glycol, polyvinyl alcohol, or povidone; and the apatite grains have a Ca to P molar ratio of 1.3 to 1.60.

41.37 (c)(1)(vi) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

THE OBVIOUSNESS REJECTIONS

A. The first obvious rejection to be reviewed is of claims 1-15, 18-20 and 72 as obvious 35 U.S.C. 103(a) as being unpatentable over Masuno Ichirou JP 64-040418 (Masuno) in view of Willi Paul et al., Porous Hydroxyapatite Nanoparticles fro Intestinal Delivery of Insulin, Trends in Biomaterials & Artificial Organs, Volume 14, number 2, 2001 pages 37-38 (Willi) and in vew of Tsuru et al EP 376331 (Tsuru) and further in view of Sapiezsco et al US 6383519 (Sapiezsco).

B. The second obvious rejection to be reviewed is of claim 16 under 35 U.S.C 103 (a) as being unpatentable over Masuno Ichirou in view of Willi Paul et al., Tsuru et al., and further in view of Troczynski.

41.37 (c)(1)(viii) ARGUMENT

THE OBVIOUSNESS REJECTIONS

Examples Of Basic Requirements of a Prima Facies Case of Obviousness

The appellant submits that the criteria set forth in the MPEP provides guidance in determining the issue of obviousness of the claims on appeal.

---SECTION---2143 Examples Of Basic Requirements of a Prima Facie Case of Obviousness

The Supreme Court in KSR International Co. v. Teleflex Inc., 82 USPQ2d 1385, 1395-97 (2007) identified a number of rationales to support a conclusion of obviousness which are consistent with the proper "functional approach" to the determination of obviousness as laid down in Graham. The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in KSR noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit. (Emphasis added.)

SECTION---2143.03 All Claim Limitations Must Be Taught or Suggested

To establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." In re Wilson, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). If an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious. In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988).

Appellants also most respectfully direct the Examiner's attention to MPEP § 2144.08 (page 2100-130) wherein it is stated that Office personnel should consider all rebuttal argument and evidence present by applicant and the citation of In re Soni for error in not considering evidence presented in the specification.

Appellants note the Examiner's comments in the Final Rejection that any differences between the prior art would have been obvious to one of ordinary skill in the art as a routine modification of the product in the absence of a showing of unexpected results does not establish a prima facie case of obviousness. This statement is tantamount to the statement that the invention was well within the ordinary skill in the art which has been found to be insufficient. A statement that

modifications of the prior art to meet the claimed invention would have been "'well within the ordinary skill of the art at the time the claimed invention was made'" because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993). **'">[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.'" *KSR*, 550 U.S. at ___, 82 USPQ2d at 1396 quoting *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006).<

THE FIRST OBVIOUSNESS REJECTION

A. The first obvious rejection to be reviewed is of claims 1-15, 18-20 and 72 as obvious 35 U.S.C. 103(a) as being unpatentable over Masuno Ichirou JP 64-040418 (Masuno) in view of Willi Paul et al., Porous Hydroxyapatite Nanoparticles fro Intestinal Delivery of Insulin, Trends in Biomaterials & Artificial Organs, Volume 14, number 2, 2001 pages 37-38 (Willi) and in vew of Tsuru et al EP 376331 (Tsuru) and further in view of Sapiezsco et al US 6383519 (Sapiezsco).

At the outset, it is to be emphasized that in evaluating the presently claimed "pharmaceutical dosage form" of the present invention, that the shape and size of the dosage form are important in addition to the structure of the dosage form in the field related to the present invention. The problems to be solved by the inventors of the present invention are how to develop a dosage form carrying a drug which can be taken by the patients orally with the taste of the drug being masked and can be stored stably. This should be borne in mind as it is part of the invention as a whole

which needs to be evaluated in determining patentability under 35 USC 103(a).

It is urged in the rejection that Masuno teaches a sustained release material for a drug, obtained by sterilizing a porous substance having biocompatibility, e.g. hydroxycalcium apatite, as an inorganic substance, 2-hydroxyethyl methacrylate of PVA as an organic substance or chitin, chitosan or collagen as a natural high polymer, dipping the sterilized porous substance in a solution of the drug dispersed in a solvent, decompressing the porous substance to remove air in pores of the porous substance, permeating the drug into all the pores and adsorbing the drug on the surface thereof. The above-mentioned sustained release material is embedded in a body to directly contact affected parts of the vicinity thereof and impart the drug effects of sustained release to affected parts (abstract).

Masuno's abstract does not include the size and surface area of the pores.

Applicants most respectfully submit that one of ordinary skill in the art would appreciate that Masuno (JP 64-040418) teaches away from the subject invention because the sustained release material taught by Masuno is to be embedded in a body and is a disk having a size of 1 mm thickness and 5 mm diameter (page 84, right bottom column, lines 6-8 from the bottom). Further, the structure of the sustained release material taught by Masuno contains a porous substance and a drug absorbed in the pores of the porous substance, wherein the porous substance is hydroxycalcium apatite, an organic substance such as PVA, or a natural high polymer such as chitosan. Masuno does not teach or suggest a structure like the subject invention where porous apatite grains are bounded by a biocompatible polymer to form a microspherical composite. Instead, Masuno teaches a single porous material lump (disk). Moreover there is no suggestion that the taste of the drug is masked or that the material is acceptable for oral administration as is the presently claimed invention due to the particle size limitations in the claims.

It is next urged that Willi teaches the encapsulation of insulin, hyaluronic acid and sodium alginate in porous hydroxyapatite wherein the pore size is less than 10 microns. This statement is specifically traversed. Willi teaches that insulin is loaded

into hydroxy apatite nanoparticles encapsulated in sodium alginate. Willi as with Masuno teaches porous hydroxyapatite nanoparticles, not a dosage form where porous apatite grains are bounded by a biocompatible polymer to form a microspherical composite dosage form which masks the taste of the drug. Therefore, it would not have been obvious to a person having ordinary skill in the art to make the dosage form set forth in claim 1 of the present application in view of Masuno and further in view of Willi, because both of these two cited references fail to teach the features of porous apatite grains being bounded by a biocompatible polymer to form a microspherical composite.

It is urged in the Final rejection that it would have been obvious to a person having ordinary skill in the art to follow the pore size disclosed by Willi since the reference has the same endeavor. This statement is traversed. Both references do not have the same purpose. Masuno teaches an embedded release agent and Willi teaches a potential release agent for insulin. It is not seen how one of ordinary skill in the art would combine the references and arrive at the presently claimed invention nor is it seen how this statement makes the rejection explicit as to the reason for the determination that the claimed subject matter is obvious in the sense of 35 USC 103.

It is acknowledged in the rejection that neither of the references teaches the Ca/P ratio and the surface area of the pores of the pores as required by the limitations of the presently claimed invention. However, it is urged that Tsuru teaches drug delivery granules comprising porous granules <u>of a calcium phosphate compound</u> having a ratio of Ca to P of 1.3 to 1.8 (examples disclose a ratio of 1.67, and 1.5), a porosity of 0.1 to 70%, a specific surface area of 0.1 to 50 m^2/g and a pore size of 1nm to 10 microns (abstract, page 3, lines 31-40 for preferable ratios and surface areas, and see also examples). The polymer comprised can be gelatin, carboxymethylchitin, glycol chitin and the like (page 4, lines 45+). The invention includes different types of the drugs such as carcinostatics, antibiotics and the like (page 4, lines 56+). It is concluded that it would have been obvious to a person

having ordinary skill in the art to use surface area and Ca/P ratio disclosed by Tsuru because both disclosures discuss the same field of art and Tsuru teaches that the drug delivery granules of the invention has a controllable and good prolonged effect of the drug release (abstract). This aspect of the rejection is traversed and should be reversed on appeal since it does not represent a fair teaching of the reference to one of ordinary skill in the art aan represents hindsight reconstruction of the claimed subject matter which, even under KSR is impermissible.

The Tsuru reference relates to calcium phosphate compounds in general, and notes apatites. Hydroxyapatite is referred to at page 5 which has a Ca/P of 1.67 which is outside of the range of 1.3 to 1.6 of claim 11 on appeal. One of ordinary skill in the art would recognize that when an apatite is used, in accordance with Tsuru, the Ca/P ratio would be outside of the presently claimed range. This represent a clear teaching away from this range. Note that the claims on appeal are limited to apatites and not to the other forms of calcium phosphate referred to in the reference as would be appreciated by one of ordinary skill in the art. Moreover, the oral dosages of the present invention are not suggested by the reference as noted in the sentence bridging pages 4 and 5 of the reference in the discussion of local injection, or implantation and transvascular chemotheraphy. None of this suggest the presently claimed invention which is unobvious over this combination of references.

Regarding the amount of polymer and/or the amount of drug loaded, since Masuno teaches that the apatite should be decompressed to remove the air from the pores, consequently, the amount of entrapped material in the pores can be controlled through this decompression and the amount of drug loading should be within the capabilities of a person of ordinary skill in the art. This statement is traversed and it is not seen how the decompression process is applicable to controlling the amount of polymer in accordance with the present invention which includes the specific amount necessary to achieve the results as set forth in Applicants' specification and working examples. This conclusion is not based on

clear explicit reasoning necessary to sustain a rejection on the grounds of obviousness.

The Examiner acknowledges "none of the references teaches the use of further biocompatible polymer," page 3, lines 3 from the bottom, the Office Action. The Examiner cites Sapeizsco and states "Sapeizsco teaches methods for the preparation of porous inorganic shaped bodies especially calcium phosphiate-containing shaped bodies. Again this represents a broad range of such compounds and there is no teaching of the apatites as claimed in the present invention. The solution is absorbed into a porous sacrificial substrate such as cellulose sponge. The shaped bodies include hydroxyapatite and are used as drug delivery vehicle." Please refer to the paragraph bridging pages 3 and 4 of the Office Action. The Examiner then in the next paragraph concluded that "it would have been obvious to one of ordinary skill in the art at the time the invention was made to add one of the poly-L-Lactic acid (PL-LA) because Sapeizsco discloses that these polymers renders the structure mass in strong, carveable, and somewhere compressible." The Examiner is wrong about the obviousness conclusion, because Sapeizsco teaches away from the dosage form set forth in claim 1 of the present invention in the way the biosorbable polymer is used as would be appreciated by one of ordinary skill in the art to which the invention pertains. As noted in the abstract of Sapeizsco, in Sapeizsco, the polymer solution is absorbed into a porous sacrificial substrate such as cellulose sponge, and in the subject invention the biocompatible polymer is between loosely porous apatite grains to bind the grains into microspherical composite. Sapeizsco does not teach one of ordinary skill in the art to modify the porous material taught by Masuno or Willi by binding the nanoparticles into microspherical composite. What Sapeizsco suggests is soaking a porous substrate with a polymer solution and heating the soaked substrate to convert it to shaped inorganic body. Accordingly, it is most respectfully requested that this rejection be reversed on appeal or withdrawn.

THE SECOND OBVIOUSNESS REJECTION

B. The second obvious rejection to be reviewed is of claim 16 under 35 U.S.C 103 (a) as being unpatentable over Masuno Ichirou in view of Willi Paul et al., Tsuru et al., and further in view of Troczynski.

For the reasons discussed above, the combination of Masuno, Willi, and Tsuru et al do not render obvious the claimed subject matter except for the specific drugs taught by Troczynski. It is urged that the cited Troczynski merely teaches hydroxyapatite microspheres that encapsulate drugs. There is no teaching related to the features of porous apatite grains being bounded by a biocompatible polymer to form a microspherical composite in the composition of claimed in claim 16. This is a claim limitation which cannot be ignored. Moreover, there is no suggestion that the taste of the drug is masked in accordance with the presently claimed invention and as clearly demonstrated for the metal gluconates, see page 12, lines 23-25 of the present specification. Again, the statement in the rejection at page 5, that the device was implanted is not relevant to the presently claimed orally administered dosage. Therefore, this rejection should be withdrawn or reversed on appeal.

IX. CONCLUSION

In view of the above arguments, all of the rejections of the claims on appeal should be reversed. The application should be passed to issue.

Respectfully submitted,

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41.37 (c)(1)(viii) Claims appendix

1. A stable and taste masked pharmaceutical dosage form comprising porous apatite grains and a drug entrapped in pores of said grains, wherein said grains have a size of 0.1-1000 μm and said pores of said grains have an opening of 0.5-300 nm, and said dosage form further comprising a biocompatible polymer, wherein said porous apatite grains are bound by said biocompatible polymer to form a microspherical composite having a size of 0.5-1000 μm.

2. The pharmaceutical dosage form according to claim 1 further comprising a water soluble polymer entrapped in pores of said grains in an amount of 0.1-10% based on the weight of the grains.

3. The pharmaceutical dosage form according to claim 1, wherein said grains have a size of 1 to 300 μm.

4. The pharmaceutical dosage form according to claim 1, wherein said pores have an opening of 1 to 200 nm.

5. The pharmaceutical dosage form according to claim 1, wherein said grains have a specific surface area of 32 to 58 m^2 per unit gram.

6. The pharmaceutical dosage form according to claim 1, wherein said drug entrapped in said porous apatite grains is in an amount of 0.1-45% based on the weight of the grains.

7. The pharmaceutical dosage form according to claim 6, wherein said drug

entrapped in said porous apatite grains is in an amount of 1-30% based on the weight of the grains.

8. The pharmaceutical dosage form according to claim 2, wherein said water soluble polymer is selected from the group consisting of chitosan, gelatin, agar, cellulose, chitin, starch, dextrin, cyclodextrin, polylactic acid, polyamino acid, polyethylene glycol, polyacrylates, hyaluronic acid, polyvinyl alcohol, povidone and mixture thereof.

9. The pharmaceutical dosage form according to claim 8, wherein said water soluble polymer is cellulose, polyethylene glycol, polyvinyl alcohol, or povidone.

10. The pharmaceutical dosage form according to claim 1, wherein said apatite grains have a Ca to P molar ratio of 1.1 to 2.1.

11. The pharmaceutical dosage form according to claim 10, wherein said apatite grains have a Ca to P molar ratio of 1.3 to 1.60.

12. The pharmaceutical dosage form according to claim 1, wherein said apatite grains contains carbonate in an amount of 0.1-40% based on the weight of the grains.

13. The pharmaceutical dosage form according to claim 12, wherein said apatite grains have a Ca to P molar ratio of 1.3 to 1.60.

14. The pharmaceutical dosage form according to claim 1, wherein said drug is a peptide, protein, enzyme, DNA, RNA, nutrient supplement agent, anti-inflammatory drug, anti-biotic drug, anti-histamine drug, anti-bacterial drug, anti-fungal drug, decongestant, anti-depressant, anti-psychotic drug, anti-viral drug, anti-

oncolytic drug, vaccine, anti-epileptic drug, anti-asthma drug, antioxidant or extract of herb.

15. The pharmaceutical dosage form according to claim 1, wherein said drug is selected from a group of zinc gluconate, copper gluconate, carbinoxzmine maleate, dextromethorphan hydrobromide, glyceryl guaiacolate, pseudoephedrine hydrochloride, triprolidrine hydrochloride, acetaminophen, aspirin, ibuprophen, dexibuprophen lysinate, naproxen, ketoprofen, lactam, quinolone, macrolide or salts thereof, loperamide, famotidine, ranitidine, cimetidine or salts thereof, ibersartan, captopril, lisinopril or salts thereof, nefzodone, buspirone or salts thereof, chlorpheniramine, astemizole, pseudoephedrine, medicon, anpirin, actirin, nidolin, ascorbic acid, hydrocortisone, 5-fluorouracil, cis-platin, paclitaxel, ampicilin, cefadroxil, clindamycin, neomycin, nystatin, polyphenol, hydroquinone, and retinal A.

16. The pharmaceutical dosage form according to claim 15, wherein said drug is zinc gluconate, copper gluconate, aspirin, ibuprophen or ascorbic acid.

18. The pharmaceutical dosage form according to claim 1, wherein said biocompatible polymer is in an amount of 0.5% to 30% based on the weight of the grains.

19. The pharmaceutical dosage form according to claim 1, wherein said biocompatible polymer is selected from the group consisting of polylactic acid, polyglycolic acid, poly(lactic-co-glycolic acid), polyanhydrates, polyethylene glycol, polyethylene oxide, polyacrylates, polymethacrylates, dextran, polysaccharides, hyaluronic acid, and mixture thereof.

20. The pharmaceutical dosage form according to claim 19, wherein said biocompatible polymer is polylactic acid, polyethylene glycol, or poly(lactic-co-glycolic acid).

72. The pharmaceutical dosage form according to claim 2, wherein said grains have a size of 1 to 300 μm; said pores have an opening of 1 to 200 nm, said grains have a specific surface area of 32 to 58 m^2 per unit gram, said drug entrapped in said porous apatite grains is in an amount of 1-30% based on the weight of the grains, wherein said water soluble polymer is cellulose, polyethylene glycol, polyvinyl alcohol, or povidone; and wherein said apatite grains have a Ca to P molar ratio of 1.3 to 1.60.

41.37 (c)(1)(ix) Evidence appendix

None

41.37 (c)(1)(x) Related proceedings appendix

None